

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



VOL. 58, No. 2

MARCH 1982

HYPERTENSION SECONDARY
TO PHEOCHROMOCYTOMA*

WILLIAM M. MANGER, M.D., Ph.D.

Chairman, the National Hypertension Association, Inc.

Associate Professor of Clinical Medicine

New York University Medical Center

New York, New York

RAY W. GIFFORD, Jr., M.D.

Head of the Department of Hypertension and Nephrology

Cleveland Clinic

Cleveland, Ohio

Clinical expressions of pheochromocytoma, often dramatic and explosive, are so variable that it has rightly earned the title of the "great mimic."¹ One cannot determine histologically whether a pheo-

* Presented as part of a *Symposium on Hypertension Update 1980: Practical Clinical Aspects* sponsored by the Section on Medicine of the New York Academy of Medicine with the National Hypertension Association, Inc. and held at the Academy May 21, 1980.

This study was supported by the National Hypertension Association, Inc., the Pew Memorial Trust, the Hearst Foundation, and the Hess Foundation.

A similar paper will appear as a chapter in *Hypertensive Cardiovascular Disease: Pathophysiology and Treatment* (publisher Martinus Nijhoff).

Address for reprint requests: William M. Manger, M.D., National Hypertension Association, Inc., 400 East 34th Street, New York, N.Y. 10016

chromocytoma is benign or malignant. Although only 10% of these neoplasms are pathologically malignant, as evidenced by metastasis or invasion of adjacent tissue, lethal complications from the effects of excessive circulating catecholamines (epinephrine and norepinephrine) almost invariably result if the disease is not appropriately treated. Every patient with manifestations that even remotely suggest pheochromocytoma must be screened for this disease.

The incidence of pheochromocytoma is unknown, but at least 0.1% of patients with persistent diastolic hypertension have this tumor. It should be remembered that about 50% of pheochromocytoma patients have only paroxysmal hypertension. Pheochromocytomas may occur at any age, but the greatest frequency occurs during the fourth and fifth decades with a slight predilection for women; among children, approximately two thirds of these tumors occur in boys.²

Pheochromocytoma arises from chromaffin cells of the sympathoadrenal system. Major sites of occurrence are the adrenal medulla, where it is located 90% of the time, the paraganglia cells of the sympathetic nervous system, and the organ of Zuckerkandl. It may also arise in the chest (<2%) and neck (<0.1%). Multiple and extra-adrenal tumors are far more common among children (35% of cases) than adults (8% of cases). Familial pheochromocytomas almost invariably arise from the adrenal medulla and are bilateral in 70% of cases or more.

Most pheochromocytomas secrete both norepinephrine and epinephrine, but norepinephrine usually predominates. Some tumors secrete only norepinephrine, and, rarely, only epinephrine may be secreted. Very rarely, dopamine, dopa, or serotonin are secreted by these tumors.³

CLINICAL PRESENTATION

Manifestations encountered in patients with pheochromocytoma are so numerous that they have been described as kaleidoscopic; about 80 manifestations have been reported.⁴ Often symptoms arise in a dramatic, explosive fashion when the tumor suddenly releases catecholamines into the circulation. Rarely, sudden death may occur during the initial attack in a patient who has been asymptomatic, or patients may present manifestations of one of the complications of these tumors. About 50% of patients with persistent hypertension have a sudden onset of symptoms, usually associated with episodic increases in hypertension; in patients with persistent hypertension symptoms are generally less pronounced than in patients with

only paroxysmal hypertension. Very rarely, a patient with either paroxysmal or sustained hypertension may remain relatively asymptomatic.⁵

Episodes may occur only once every few months or as often as 25 times daily and persist for from less than a minute to as long as one week. Paroxysms may also occur daily at the same time but are usually quite irregular. About 75% of patients with pheochromocytoma experience one or more attacks weekly, and the remainder have one or more daily.⁶ Attacks invariably subside more slowly than they start. They may be elicited by any of the following factors: massage or steady pressure for a minute or two in the area of the tumor; lying in a particular position; postural changes, especially involving flexion and bending of the body; exercise; anxiety; having the blood pressure taken; eating, ingestion of certain foods or alcoholic beverages that contain tyramine (e.g., cheese, beer, and wine) or of fruit juice rich in synephrine; hyperventilation; increased intra-abdominal pressure; parturition; the Valsalva maneuver; tight clothing; laughing; pressure on the carotid sinuses; certain odors; micturition; bladder distention; straining at stool; smoking a cigarette; shaving; gargling; sneezing; sexual intercourse; trauma; pain; changes in body temperature; intramuscular or subcutaneous administration of certain drugs such as histamine, glucagon, epinephrine, tyramine, tetraethylammonium, methacholine, succinylcholine chloride (Anectine), nicotine, adrenocorticotrophic hormone (ACTH), phenothiazines, or saralasin and other angiotensin II analogs; and intubation, anesthesia, or operative manipulation.

Symptoms. Symptoms of pheochromocytoma are due either to pharmacologic effects of excessive circulating catecholamines or to complications of hypertension. Table I cites the symptoms, of which the three most commonly experienced are headache, generalized sweating, and palpitations. Additional manifestations due to complications or coexisting diseases or syndromes are also listed in Table I.

Headaches are almost always paroxysmal, frequently throbbing and bilateral, and usually very severe during a paroxysm of hypertension. Abrupt in onset, they subside as blood pressure returns toward normal; frequently they are accompanied by nausea and vomiting. Often they are occipital or frontal or both in location, but at times are generalized and characterized by an intense sensation or pressure, occasionally including throbbing in the temporal regions. Some patients are awakened by severe headache in the early morning. Although headache may be severe in pa-

TABLE I. SYMPTOMS REPORTED BY PATIENTS WITH
PHEOCHROMOCYTOMA ASSOCIATED WITH PAROXYSMAL
OR PERSISTENT HYPERTENSION*

<i>Symptoms presumably due to excessive catecholamines or hypertension</i>	<i>Paroxysmal (37 patients)</i>	<i>Persistent (39 patients)</i>
Headaches (severe)	92†	72†
Excessive sweating (generalized)	65	69
Palpitations ± tachycardia	73	51
Anxiety or nervousness (± fear or impending death, panic)	60	28
Tremulousness	51	26
Pain in chest, abdomen (usually epigastric). lumbar regions, lower abdomen, or groin	48	28
Nausea ± vomiting	43	26
Weakness, fatigue, prostration	38	15
Weight loss (severe)	14	15
Dyspnea	11	18
Warmth ± heat intolerance	13	15
Visual disturbances	3	21
Dizziness or faintness	11	3
Constipation	0	13
Paresthesia or pain in arms	11	0
Bradycardia (noted by patient)	8	3
Grand mal	5	3
Miscellaneous (A large number of miscellaneous symptoms have been reported. Especially noteworthy are painless hematuria, frequency, nocturia, and tenesmus in pheochromocytoma of the urinary bladder.)		
<i>Manifestations due to complications</i>		
Congestive heart failure ± cardiomyopathy		
Myocardial infarction		
Cerebrovascular accident		
Ischemic enterocolitis ± megacolon		
Azotemia		
Dissecting aneurysm		
Encephalopathy		
Shock		
Hemorrhagic necrosis in a pheochromocytoma		
<i>Manifestations due to coexisting diseases or syndromes</i>		
Cholelithiasis		
Medullary thyroid carcinoma ± effects of secretions of serotonin, calcitonin, prostaglandin, or ACTH-like substance		
Hyperparathyroidism		
Mucocutaneous neuromas with characteristic facies		
Thickened corneal nerves (seen only with slit lamp)		
Marfanoid habitus		
Alimentary tract ganglioneuromatosis		
Neurofibromatosis and its complications		
Cushing's syndrome (rare)		
von Hippel-Lindau disease (rare)		
Virilism, Addison's disease, acromegaly (extremely rare)		
<i>Symptoms caused by encroachment on adjacent structures or by invasion and pressure effects of metastases</i>		

*Total of 76 patients, almost all adults

†Approximate percent

Reproduced with permission from Manger, W. M. and Gifford, R. W., Jr.: Current concepts of pheochromocytoma. *Cardiovasc. Med.* 3:292, 1978.

tients with sustained hypertension, sometimes they are mild to moderate and indistinguishable from tension headaches and those described by patients with essential hypertension.

About two thirds of our patients have had excessive perspiration, sometimes "drenching" in nature, that was generalized, but more so in the upper body and not confined to one area. The most profuse sweating appears during paroxysmal attacks of hypertension, but it may appear as the crisis recedes. Palpitations, the third most common symptom, are usually accompanied by tachycardia, although reflex bradycardia may be elicited by the increased blood pressure. Patients frequently complain of "pounding" in the chest.

Signs. The clinical signs of pheochromocytoma encountered in 76 patients are cited in Table II.

In 138 patients with pheochromocytoma seen at the Mayo Clinic, 91% had hypertension; in 42% hypertension was paroxysmal, whereas in 49% it was sustained.⁷ A small percentage of pheochromocytomas may cause manifestations other than hypertension. Some tumors cause no signs or symptoms, either because they are nonfunctioning or because they release only relatively small amounts of catecholamines into the circulation; these tumors may be found accidentally by roentgenographic examination at operation or at autopsy.⁸⁻¹⁰

The type of hypertension tends to be consistent in members of a family afflicted with pheochromocytoma, i.e., all family members harboring the tumor have sustained hypertension or all have paroxysmal hypertension.⁵ A few patients have hypotensive episodes, sometimes alternating with hypertension. During a paroxysm of hypertension, blood pressure may on rare occasions be unobtainable with a sphygmomanometer because of severe peripheral vasoconstriction. Orthostatic hypotension in a hypertensive patient not being treated with antihypertensive medication suggests pheochromocytoma. Some have claimed that orthostatic hypotension occurs in 70% of patients with sustained hypertension caused by this tumor.^{11,12}

A paradoxical blood pressure response to certain antihypertensive drugs, (ganglionic blocking agents, propranolol, guanethidine) and a marked pressor response frequently observed during induction with almost any anesthetic agent should also suggest pheochromocytoma.²

Although pallor of the face and upper part of the body has been observed in 60 to 28% of patients having paroxysmal and sustained hypertension, respectively, flushing of the face may rarely be observed alone or following the pallor.²

TABLE II. SIGNS OBSERVED IN PATIENTS* WITH PHEOCHROMOCYTOMA

Blood pressure changes

± Hypertension ± wide fluctuations (rarely, paroxysmal hypotension or hypertension alternating with hypotension)
 Hypertension induced by physical maneuver such as exercise, postural change, or palpation and massage of flank or mass elsewhere
 Orthostatic hypotension ± postural tachycardia
 Paradoxical blood pressure response to certain antihypertensive drugs and marked pressor response with induction or anesthesia

Other signs of catecholamine excess

Hyperhidrosis
 Tachycardia or reflex bradycardia; very forceful heartbeat; arrhythmia
 Pallor of face and upper part of body (rarely flushing)
 Anxious, frightened, troubled appearance
 Hypertensive retinopathy
 Dilated pupils (very rarely exophthalmos, lacrimation, scleral pallor or injection; pupils may not react to light)
 Leanness or underweight
 Tremor (± shaking)
 Raynaud's phenomenon or livedo reticularis (occasionally puffy, red, cyanotic hands in children); skin of extremities wet, cold, clammy, pale; gooseflesh; occasionally, cyanotic nail beds
 Fever

Mass lesion

Palpable tumor in abdomen (rare), neck pheochromocytoma or chemodectoma, thyroid carcinoma, or thyroid swelling (very rare and only during hypertensive paroxysm)

*Signs caused by encroachment on adjacent structures or by invasion and pressure effects of metastases**Manifestations related to complications or coexisting diseases or syndromes (see Table I)*

*Total of 76 patients, almost all adults

Reproduced by permission from Manger, W. M. and Gifford, R. W., Jr.: Current concepts of pheochromocytoma. *Cardiovasc. Med.* 3:293, 1978.

Retinopathy, of Group 3 or 4 classification,¹³ was found in about half of our patients with persistent hypertension due to pheochromocytoma, but was indistinguishable ophthalmologically from that seen in primary hypertension. Retinopathy was not observed in patients with paroxysmal hypertension.²

Atypical manifestations. When pheochromocytoma occurs during childhood or pregnancy or if the tumor arises in the urinary bladder, atypical manifestations are frequently evident.

It is important to measure the blood pressure routinely in children, because more than 90% of those with pheochromocytoma have sustained hypertension. Visual complaints, nausea, vomiting, and weight loss occur more frequently among children than among adults. A puffy, red, cyanotic appearance of the hands is occasionally seen in children, but not in adults.²

Pregnancy complicated by pheochromocytoma may be confused with toxemia of pregnancy, preeclampsia, or a ruptured uterus when the patient goes into shock during or immediately after labor.¹⁴ Attacks may be aggravated by pregnancy in some patients, whereas in others attacks may subside during pregnancy.

Pheochromocytomas of the urinary bladder frequently cause paroxysmal attacks which occur during or shortly after micturition or with distention of the bladder; 65% of patients have painless hematuria.¹⁵

ENTITIES SOMETIMES ASSOCIATED WITH PHEOCHROMOCYTOMA

Conditions occurring more frequently among patients with pheochromocytoma than the general population should be kept in mind.

Familial pheochromocytoma associated with multiple endocrine neoplasms or hyperplasia of the thyroid and parathyroids was originally designated MEN (multiple endocrine neoplasia) type 2.⁵ Development of neoplasms in other endocrine glands or the presence of multiple endocrine neoplasia in relatives establishes the diagnosis. Coexistence of pheochromocytoma, medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, alimentary tract ganglioneuromatosis, and frequently a marfanoid habitus constitutes still another familial entity, MEN type 3,¹⁶ also designated type 2B or 2b (Figure 1).¹⁷⁻²⁰ Hyperparathyroidism occurs in about 50% of patients with MEN type 2 but is rare in MEN type 3.¹⁶

The increased incidence of cholelithiasis (up to 30%) among patients with pheochromocytoma remains unexplained.²

Association of neurocutaneous lesions with pheochromocytoma is best explained by the fact that these lesions are of neuroectodermal origin. Neurofibromatosis (von Recklinghausen's disease) with or without café-au-lait spots occurs in 5% of patients with pheochromocytoma; the incidence of pheochromocytoma in neurofibromatosis is less than 1%.²¹ Vascular anomalies (coarctation, renal artery stenosis, or renal artery aneurysm) sometimes occur with neurofibromatosis and may cause hypertension.² Rarely, pheochromocytoma occurs in association with von Hippel-Lindau disease (cerebellar hemangioblastoma and retinal angioma) or acromegaly.

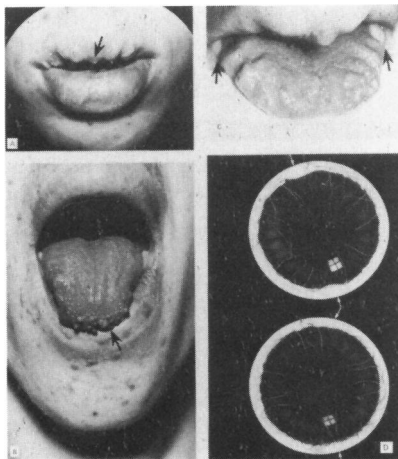


Fig. 1. Lesions of the lips, tongue, and corneas, observed in five patients with multiple endocrine neoplasia, type 3. A. Diffuse thickening of lower lip, which is everted and patulous. Thickening of upper lip is less prominent but is irregular and accentuated centrally (arrow) and produces a bumpy appearance. Medullary thyroid carcinomas and pheochromocytomas occurred in this patient. B. Multiple sessile confluent nodules stud tip of tongue. Slightly elevated plaquelike lesions, more evident on right (arrow), are present along margins of tongue. Upper lip is diffusely thickened. Similar alteration of lower lip is concealed by tongue. Medullary thyroid carcinoma was present without evidence of pheochromocytoma. C. Several large nodules are present on anterior third of tongue. Lateral margin exhibits a coarse undulating (left) and bumpy (right) appearance. Intraoral conical projections at angles of mouth are just visible bilaterally (arrows). Upper lip is diffusely thickened and exhibits characteristic central accentuation of thickening. Medullary thyroid carcinoma was present without evidence of pheochromocytoma. Thickened corneal nerves of right and left eyes of a patient with MEN-type 3. Thickened perilimbal neuromas are visible on either side of each limbus (see arrows). This drawing by Dr. Dennis M. Robertson was based on the precise location of corneal nerves and neuromas determined by sequential slit-lamp examination of the entire cornea. Reproduced by permission from Carney, J. A., Sizemore, G. W., and Lovestedt, S. A.: Mucosal ganglioneuromatosis, medullary thyroid carcinoma, and pheochromocytoma: Multiple endocrine neoplasia, type 2b. *Oral Surg.* 41: 746, 747, 1976; Robertson, D. M., Sizemore, G. W., and Gordon, H.: Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 79: 773, 1975; Manger, W. M. and Gifford, R. W., Jr.: *Pheochromocytoma*. New York, Springer-Verlag, 1977.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of pheochromocytoma, the clinician may have to consider the disease entities listed in Table III. Preoperative diagnosis must be confirmed by significant elevations of catecholamines or their metabolites in the urine or plasma. A careful history and physical examination can be of great value in deciding which patients with sustained or paroxysmal hypertension to screen for pheochromocytoma, because approximately 95% are symptomatic.

TABLE III. DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA*

All hypertensive states (sustained and paroxysmal)
Anxiety, tension states, psychoneurosis, psychosis
Hyperthyroidism
Paroxysmal tachycardia
Hyperdynamic beta-adrenergic circulatory state
Menopause
Vasodilating headache (migraine and cluster headaches)
Coronary insufficiency syndrome
Acute hypertensive encephalopathy
Diabetes mellitus
Renal parenchymal or renal arterial disease with hypertension
Focal arterial insufficiency of the brain
Intracranial lesions (\pm \uparrow intracranial pressure)*
Autonomic hyperreflexia*
Diencephalic seizure and syndrome
Toxemia of pregnancy (or eclampsia with convulsions*)
Hypertensive crises associated with monoamine oxidase inhibitors
Carcinoid*
Hypoglycemia*
Mastocytosis
Familial dysautonomia
Acrodynia*
Neuroblastoma, * ganglioneuroblastoma, * ganglioneuroma*
Acute infectious disease
Rare causes of paroxysmal hypertension (acute porphyria, acute lead poisoning, clonidine withdrawal, tetanus, Guillain-Barre syndrome, factitious, etc.)*
Fortuitous circumstances simulating pheochromocytoma such as coarctation of the abdominal aorta, renal cyst, and adrenocortical adenoma with hypertension

*Conditions reported to cause occasional increased excretion of catecholamines or their metabolites or both

Reproduced by permission from Manger, W. M. and Gifford, R. W., Jr.: Current concepts of pheochromocytoma. *Cardiovascular Medicine* 3:293, 1978.

All symptomatic patients with sustained or paroxysmal hypertension should be screened unless the cause of their hypertension is known; asymptomatic patients with hypertension of unknown cause should be screened if they have diseases known occasionally to occur with pheochromocytoma or abnormal laboratory findings that may be caused by increased circulating catecholamines.

Conditions that may be accompanied by hypertension and an increased urinary excretion of catecholamines or their metabolites have been starred in Table III. Clinical manifestations suggesting pheochromocytoma in a person having access to vasopressor drugs should suggest the remote possibility of factitious production of symptoms, i.e., pseudopheochromocytoma.²²

TABLE IV. INDICATIONS FOR SCREENING PATIENTS FOR PHEOCHROMOCYTOMA

Hypertensives (sustained or paroxysmal) with:

Symptoms (see Table I) and/or signs (see Table II)
 Group 3 or 4 retinopathy of unknown cause
 Weight loss
 Hyperglycemia
 Hypermetabolism without hyperthyroidism

Persons with marked hyperlability of blood pressure

Recurrent attacks of symptoms (see Table I) and signs (see Table II), even if hypertension not demonstrated.

Severe pressor response during or induced by:

Anesthesia induction
 Surgery
 Angiography
 Parturition
 Antihypertensive therapy
 Factors listed under "Clinical Presentation"

Unexplained circulatory shock

During anesthesia
 During pregnancy, delivery, or in puerperium
 During operation or postoperatively
 Following administration of phenothiazine drugs
 Family history of pheochromocytoma, especially if hypertensive (also screen siblings and children)
 Hypertensives with diseases sometimes associated with pheochromocytoma (see Table I)
 Apparent toxemia of pregnancy with hyperlabile blood pressure or severe hypertension
 Transient abnormal electrocardiogram during hypertensive episodes
 X-ray evidence of suprarenal mass

Finally, the extreme importance of recognizing hemorrhagic necrosis in a pheochromocytoma cannot be overstated. This condition may mimic an acute abdomen or a cardiovascular catastrophe, and without prompt treatment and extirpation of the tumor the patient will almost certainly die.

DIAGNOSIS

Guidelines for screening patients for pheochromocytoma are given in Table IV, and certain facts worth emphasizing and memorizing are listed in Table V.

TABLE V. PHEOCHROMOCYTOMA FACT SHEET

<i>MEN-type 3 sextet</i>	<i>Rough rule of 10</i>
Medullary thyroid carcinoma	10% familial
Bilateral familial pheochromocytoma (frequent)	10% bilateral (adrenal)*
Mucosal neuromas	10% malignant
Thickened corneal nerves	10% multiple
Marfanoid habitus	(other than bilateral adrenal)*
Alimentary tract ganglioneuromatosis	10% extra-adrenal*
(Very rarely, hyperparathyroidism)	10% occur in children
<i>The 5 H's</i>	<i>The 4 C's</i>
Hypertension	Cholelithiasis
Headache	Cushing's syndrome (rare)
Hyperhidrosis	Cutaneous lesions
Hypermetabolism	Cerebellar hemangioblastoma (rare)
Hyperglycemia	<i>Pheochromocytoma manifestations may appear during pregnancy!</i>
<i>95% of patients will have one or more of the following:</i>	<i>MEN-type 2 triad</i>
Headache	Medullary thyroid carcinoma
Hyperhidrosis	Bilateral familial pheochromocytoma (frequent)
Palpitation	Hyperparathyroidism (~50%)

*Adults and children combined; MEN = multiple endocrine neoplasia
 Reproduced by permission from Manger, W. M. and Gifford, R. W., Jr.: Current concepts of pheochromocytoma. *Cardiovas. Med.* 3:298, 1978.

Laboratory and electrocardiographic findings. The following laboratory abnormalities may be helpful clues to pheochromocytoma: hyperglycemia, impaired glucose tolerance, glycosuria, hypermetabolism, and increased free fatty acids. Rarely, polycythemia, transitory leukocytosis, or hyperreninemia may occur. Further, when a patient with pheochromocytoma has a coexisting disease or complication (see Table I), other abnormal laboratory findings may be reported. A wide variety of abnormal electrocardiographic findings have been reported among patients with pheochromocytoma; they are non-specific, but appearance of electrocardiographic changes during paroxysmal hypertension and their reversibility with subsidence of the paroxysm suggests pheochromocytoma, especially in the absence of another cause.²

Pharmacologic tests. Rarely is there need for performing a phentolamine test; however, when a patient presents in a hypertensive crisis or with sustained malignant hypertension, the blood pressure response to intravenous phentolamine may help in the differential diagnosis. False-positive phentolamine test results may be obtained in some patients with malignant hyper-

tension.² Occasionally, glucagon or histamine provocative tests, combined with chemical quantitation of urine or plasma catecholamines or their metabolites, prove indispensable to the diagnosis of a paroxysmally secreting pheochromocytoma. Adequate precautions to counteract hypertensive crises, arrhythmias, or hypotension must be observed when performing provocative tests. Provocative tests are safe if performed correctly and with proper precautions.² Provocative tests should be performed or supervised by one thoroughly familiar with the procedure, preferably in a hospital setting.

Biochemical tests. The sine qua non for preoperative diagnosis of pheochromocytoma is demonstration of elevated catecholamines or their metabolites in urine or plasma. Exploratory surgery without chemical confirmation or radiologic evidence of a tumor is indefensible. Patients with pheochromocytoma who have sustained hypertension due to excessive circulating catecholamines invariably have elevated plasma and urinary catecholamines or metabolites. Rarely, some patients have normal concentrations of catecholamines and their metabolites when the blood pressure is normal; when evaluating these patients, it is imperative that plasma or urine be obtained during a hypertensive period, either occurring spontaneously or induced by a provocative agent, because occasionally preoperative diagnosis can be made only using this approach.

Measurement of total metanephrines (metanephrine plus normetanephrine) in a 24-hour urine specimen has proved the most reliable method to detect pheochromocytoma. More than 95% of patients have elevated excretion of total metanephrines; further, quantitation of total metanephrines is comparatively easy, and fewer drugs interfere with its assay than with assays of urinary catecholamines or vanilmandelic acid. Substances that can interfere with quantitation of urinary catecholamines or their metabolites are listed in Table VI, which also cites the upper limit of normal concentrations in adults. It is essential that drugs significantly altering urinary assays be avoided for at least one full week before urine specimens are collected. We are unaware of any patients with pheochromocytoma in whom drug therapy lowered the excretion rate of the catecholamines or their metabolites to a normal range. Severe renal insufficiency may possibly result in markedly impaired excretion of catecholamines and their metabolites.

Patients requested to collect 24-hour urine specimens for assay should be instructed to avoid severe stress (e.g., strenuous physical activity or ex-

posure to extreme cold) during the collection period, because stress may significantly elevate levels of the substances assayed.

The finding that a significant fraction of urinary catecholamines is epinephrine or its metabolite metanephrine, or that plasma epinephrine is elevated, strongly suggests that the pheochromocytoma is located in the adrenal area; rarely, tumors secreting significant amounts of epinephrine have occurred in extra-adrenal sites.²

Preoperative location of pheochromocytoma. In addition to demonstrating increased concentrations of epinephrine or metanephrine in urine or plasma, suggesting an intra-adrenal tumor, radiography and central venous blood sampling for catecholamine assay can be of great value in locating the site of pheochromocytoma. Nephrotomography successfully located 67% of abdominal pheochromocytomas.⁷ Angiography (i.e., aortography, selective arteriography, and adrenal phlebography) is exceptionally valuable in locating pheochromocytomas and has the advantage of demonstrating vascular abnormalities in many intra-adrenal and extra-adrenal tumors. Aortography almost always demonstrates adrenal pheochromocytomas that are large and well vascularized. However, sometimes only selective arteriography or adrenal phlebography will demonstrate the tumor. Computerized axial tomography appears as reliable as angiography in detecting adrenal and extra-adrenal pheochromocytomas (Figure 2).^{2,3} Angiography and computerized axial tomography can be of great value in locating tumors in the thorax and neck. Oblique chest roentgenograms should be obtained routinely when pheochromocytoma is considered, because these tumors usually are located near the spine.

Controversy exists whether alpha-adrenergic blockade should be induced in all patients suspected of harboring a pheochromocytoma prior to angiography to avoid hypertensive crises precipitated by injection of contrast media. In most instances patients should be blocked during angiographic studies. However, a prior negative exploratory laparotomy is an indication for avoiding adrenergic blockade, because a hypertensive response during selective arteriography can be an important aid in confirming the diagnosis and in locating the tumor. Appropriate precautions must be taken to treat hypertensive crises, arrhythmias, or hypotension if angiography is performed in an unblocked patient.

When feasible, vena cava catheterization and central venous blood sampling for catecholamine assay, followed by adrenal phlebography, should be performed when pheochromocytoma has not been located by

TABLE VI. EFFECTS OF DRUGS AND INTERFERING SUBSTANCES
ON CONCENTRATIONS OF URINARY CATECHOLAMINES
AND METABOLITES*

	<i>Upper limit of normal range (adult) (mg./24 hr.)</i>	<i>Effects of drugs and interfering substances</i>
Catecholamines		<i>Increase apparent value</i>
Epinephrine	0.02	Catecholamines
Norepinephrine	0.08	Drugs containing catecholamines
Total	0.10	Isoproterenol†
Dopamine	0.20	L-dopa
		Methyldopa
		Tetracyclines†
		Erythromycin†
		Chlorpromazine†
		Other fluorescent substances† (e.g., quinine, quinidine, bile in urine)
		? rapid clonidine withdrawal ethanol
		<i>Decreases apparent value</i>
		Fenfluramine (large doses)
Metanephrines		<i>Increase apparent value</i>
Metanephrine	0.4	Catecholamines
Normetanephrine	0.9	Drugs containing catecholamines
Total	1.3	MAO inhibitors
		Benzodiazepines
		?rapid clonidine withdrawal ethanol
		<i>Decreases apparent value</i>
		Methylglucamine (in Renovist, Renografin, etc.)
		Fenfluramine (large doses)
VMA		<i>Increase apparent value</i>
(vanillylmandelic acid)	6.5	Catecholamines (minimal increase)
		Drugs containing catecholamines (minimal increase)
		L-dopa
		Nalidixic-acid†
		? rapid clonidine withdrawal
		<i>Decrease apparent value</i>
		Clofibrate
		Disulfiram
		Ethanol
		MAO inhibitors
		Fenfluramine (large doses)

*As determined by most reliable assays

†Probably spurious interference

? = uncertain if significant increase can occur

MAO = monoamine oxidase

Reproduced by permission from Manger, W. M. and Gifford, R. W., Jr.: Current concepts of pheochromocytoma. *Cardiovasc. Med.* 3:303, 1978.

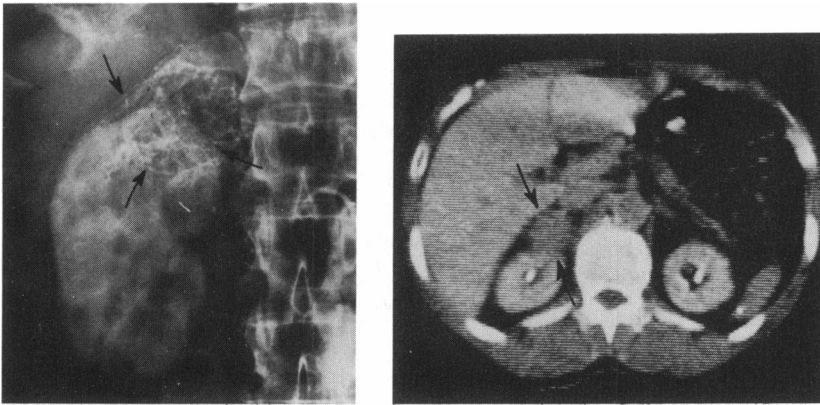


Fig. 2. Demonstration of a pheochromocytoma in the right adrenal gland by (A) angiography (note vascularity of tumor above right kidney) and (B) computerized axial tomography (arrows, indicate tumor location). Courtesy of Dr. Thomas Meaney, Cleveland Clinic Foundation.

other radiographic procedures. Central venous sampling can be particularly helpful when tumors are very small, multiple, or metastatic; it usually permits exclusion of cervical or intrathoracic pheochromocytoma. Although we have not found it necessary to induce alpha-adrenergic blockade prior to catheterization for blood sampling, the precautions recommended for angiography in unblocked patients should be observed.

TREATMENT

Preoperative evaluation and management. Expertise and teamwork are essential to successful management of pheochromocytoma. Preoperatively, one must exclude other conditions that may increase excretion of catecholamines and their metabolites. If evidence suggests familial pheochromocytoma, it is mandatory to determine if medullary thyroid carcinoma or hyperparathyroidism is present. Cushing's syndrome in patients with pheochromocytoma requires preoperative evaluation, but ACTH infusion tests, if indicated, should be performed with extreme caution because of the risk of severe hypertensive crises.⁵ Malignant pheochromocytomas may metastasize, and metastatic lesions should be identified whenever possible. Angiographic studies can provide the surgeon with a vascular "road map" that may aid in removal of the tumor. If pheochromocytoma in the urinary bladder is suspected, cystoscopy should be carried out under alpha-adrenergic blockade.

Any diagnostic procedure, including abdominal palpation, that entails

even minor trauma or stress should be performed with caution and with drugs immediately at hand to treat hypertensive crises, arrhythmias, or hypotension.

Occasionally, patients with pheochromocytoma may present with acute or malignant hypertension or with acute abdominal or cardiovascular complications requiring immediate medical and surgical therapy. In managing an acute hypertensive crisis, either before or during surgery or induced by angiography or a provocative test, we usually use rapid injections of phentolamine, giving 5 mg. at a time but leaving the needle and syringe in place so that if there is no response within a minute or two another 5 mg. can be given and repeated until the crisis is brought under control. Because the effect of phentolamine is transient, it may be necessary, especially during spontaneous crises and during operation, to control blood pressure by infusing phentolamine or sodium nitroprusside (usually 100 mg. of either drug mixed with 500 ml. of 5% dextrose in water) at a rate adequate to keep blood pressure within a relatively normal range. In the presence of impaired renal function or with prolonged infusion of nitroprusside, the thiocyanate level in the blood should be monitored, because concentrations >10 mg. per deciliter may cause toxic psychosis.

Preoperative and intraoperative management remains controversial. Advocates of preoperative alpha-adrenergic blockade continued to the time of operation argue that blockade prevents severe preoperative clinical manifestations, reverses the hypovolemia that frequently exists, and promotes smooth induction of anesthesia and a relatively stable blood pressure during operation. Those who oppose alpha-adrenergic blockade up to the time of operation feel that if blockade is complete, the surgeon will not have the advantage of utilizing increases in blood pressure as a guide to tumor location or of immediately recognizing, by persistence of hypertension, that another tumor may be present. Although preoperative alpha-adrenergic drugs in moderate dosage are indicated if sustained hypertension or paroxysmal attacks are very severe or if the patient is precariously ill, we feel that complete blockade is contraindicated, especially when the location of the tumor is uncertain or when multiple tumors are anticipated. To induce alpha-adrenergic blockade we recommend starting with 10 mg. of phoxybenzamine twice daily and increasing the dosage with gradual increments, usually to 20 to 40 mg. two or three times a day, until an optimal dosage is obtained as judged by blood pressure control.

Prazosin hydrochloride selectively blocks postsynaptic alpha receptors and is effective in controlling hypertension due to pheochromocytoma.²⁴

Patients with pheochromocytoma frequently are unusually sensitive to prazosin and we recommend starting with 0.5 mg., which may control the hypertension for 8 to 12 hours. Severe pheochromocytic hypertension often can be controlled with 1 or 2 mg. of prazosin two or three times daily. Prazosin can be used for preoperative alpha-adrenergic blockade and probably will become the drug of choice if further experience indicates that it is as effective as phenoxybenzamine and produces fewer side-effects.

Preoperative beta-adrenergic blockade with propranolol is indicated in the presence of persistent tachycardia or arrhythmias that appear hazardous or if angina pectoris occurs, provided there are no contraindications to its use. *Propranolol should never be given to a patient with pheochromocytoma without first creating alpha-adrenergic blockade* because beta blockade, even in the presence of alpha blockade, may significantly elevate blood pressure. To induce beta blockade, 10 mg. of propranolol is given twice daily and increased by 10 mg. increments every day or two, usually to 40 mg. two or three times daily, until the tachycardia or arrhythmia is controlled. The intravenous administration of a bolus of propranolol (0.5 mg. in 15 to 30 seconds) or lidocaine (50 to 100 mg.) may be required to correct significant arrhythmias.²

Labetalol, a drug with both alpha-and beta-adrenergic blocking action, was reported effective orally or intravenously in controlling blood pressure and clinical manifestations in some patients with pheochromocytoma.²⁵

In expert hands operative mortality (0 to 3.3%) does not appear to have been influenced by preoperative alpha-and beta-adrenergic blockade.²

Certain drugs (morphine, droperidol, phenothiazines) should be avoided because they may precipitate hypertensive crises or hypotension. If bilateral adrenalectomy is anticipated, appropriate steroid replacement therapy should be instituted before operation.²

Operative and postoperative management and follow-up. Careful monitoring of arterial pressure, electrocardiogram, and central venous pressure is crucial to successful intraoperative management. Intubation must be performed with appropriate premedication. Enflurane or halothane appear to be suitable anesthetic agents.² Prompt control of hypertensive crises and arrhythmias during operation is critical; appropriate use of phentolamine, sodium nitroprusside, propranolol, lidocaine, and volume expanders has been discussed in detail elsewhere.² Of paramount importance in preventing postoperative hypotension is preoperative and intraoperative correction of blood volume deficits; vasopressor agents are rarely indicated.

The anterior transperitoneal approach is mandatory when operating for

an intra-abdominal pheochromocytoma because these tumors may be multiple and extra-adrenal. Surgical strategy varies but we believe the desirable strategy is immediate ligation of tumor blood vessels followed by extirpation and thorough exploration for residual tumors.² Because of high incidence of coexisting cholelithiasis, the gallbladder should be examined during exploration and removed if indicated.

Pheochromocytomas in the neck and chest require specialized surgical techniques, but preoperative, intraoperative, and postoperative management is similar to that described for intraabdominal tumors. Management of pregnant patients depends somewhat on the duration of pregnancy when a diagnosis of pheochromocytoma is made. In early pregnancy, extirpation of the tumor has been recommended, whereas in the later months of pregnancy, patients may be treated with adrenergic blocking agents as indicated until close to term.²⁶ We consider it best to remove a pheochromocytoma as soon as it is discovered, regardless of the duration of pregnancy. If pregnancy is carried to term, we recommend cesarean section with tumor extirpation without exposing the patient to the stress of vaginal delivery.²

Monitoring and close observation should continue postoperatively until the patient's condition is stable. Bleeding at operative sites may well cause postoperative hypotension. Postoperative hypertension may result from fluid overload, pain, residual pheochromocytoma, or inadvertent ligation of a renal artery. Severe hypoglycemia, sometimes leading to central nervous system manifestations with coma, has been reported in several patients within two hours postoperatively; it is a transient phenomenon, perhaps due to increased insulin release, and should be treated by infusion of dextrose in water.^{27,28}

The five-year survival rate of patients with benign tumors is 96%, whereas it drops to 44% for patients with malignant pheochromocytomas.⁷ Approximately 75% of patients are normotensive following surgical removal, while the remainder have sustained hypertension without evidence of residual tumor. The cause of this sustained hypertension remains uncertain.

Chronic medical management. If a pheochromocytoma has metastasized or cannot be totally resected, one must remove as much of the tumor as possible to reduce functioning tissue to a minimum. Radiotherapy and chemotherapy have usually proved relatively ineffective. By blocking peripheral effects of catecholamines, chronic medical treatment with phenoxybenzamine has proved very successful in controlling blood pressure and

manifestations of excessive circulating catecholamines. Alpha-methyl-L-tyrosine (Demser) has been used effectively to decrease synthesis of catecholamines in patients with pheochromocytoma; unfortunately, it can cause serious side-effects.

ACKNOWLEDGMENTS

The valuable and very expert assistance of Mildred Hulse and Margaret Forsyth is gratefully acknowledged.

REFERENCES

1. Decourcy, J.L. and Decourcy, C.B.: *Pheochromocytomas and the General Practitioner*. Cincinnati, Barclay Newman, 1952.
2. Manger, W.M. and Gifford, R.W., Jr.: *Pheochromocytoma*. New York, Springer-Verlag, 1977.
3. Winkler, H. and Smith, A.D.: Pheochromocytomas and Other Catecholamine-producing Tumors. In: *Catecholamines*, Blaschko, H. and Muscholl, E. editors. New York, Springer-Verlag, 1972, pp. 900-33.
4. Hermann, H. and Mornex, R.: *Human Tumors Secreting Catecholamines: Clinical and Physiopathological Study*. Oxford, Pergamon Press, 1964.
5. Steiner, A.L., Goodman, A.D., and Powers, S.R.: Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia type 2. *Medicine* 37:371-409, 1968.
6. Thomas, J.E., Rooke, E.D., and Kvale, W.F.: The neurologist's experience with pheochromocytoma. A review of 100 cases. *J.A.M.A.* 197:754-58, 1966.
7. Remine, W.H., Chong, G.C., van Heerden, J.A., et al.: Current management of pheochromocytoma, *Ann. Surg.* 179:740-48, 1974.
8. Minno, A.M., Bennett, W.A., and Kvale, W.F.: Pheochromocytoma; a study of 15 cases diagnosed at autopsy. *N. Engl. J. Med.* 251:959-65, 1954.
9. Aranow, H. Jr.: Pheochromocytoma. In: *Monographs in Medicine*. Bean, W.E., editor. Baltimore, Williams and Wilkins, 1952, p 179.
10. Taubman, I., Pearson, O.H., and Anton, A.H.: An asymptomatic catecholamine-secreting pheochromocytoma. *Am. J. Med.* 57:953-56, 1974.
11. Sjoerdsma, A.: Sympatho-adrenal System: Pheochromocytoma. In: *Cecil Loeb Textbook of Medicine*. Beeson, P.B. and McDermott, W.: editors. Philadelphia, Saunders, 1971, 13th ed., pp. 1832-36.
12. Engelman, K., Zelis, R., Waldmann, T., et al.: Mechanism of orthostatic hypotension in pheochromocytoma. *Circulation* 38 (Suppl. 6): 72, 1968.
13. Keith, N.M., Wagener, H.P., and Barker, N.W.: Some different types of essential hypertension: their course and prognosis. *Am. J. Med. Sci.* 197:332-43, 1939.
14. Hume, D.M.: Pheochromocytoma in the adult and in the child. *Am. J. Surg.* 99:458-96, 1960.
15. Leestma, J.E. and Price, E.B., Jr.: Paraganglioma of the urinary bladder. *Cancer* 28:1063-73, 1971.
16. Khairi, M.R., Dexter, R.N., Burzynski, N.J., and Johnston, C.C., Jr.: Mucosal neuroma, pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine* 54:89-112, 1975.
17. Carney, J.A., Go, V.L., Sizemore, G.W., and Hayles, A.B.: Alimentary-

- tract ganglioneuromatosis. A major component of the syndrome of multiple neoplasia, type 2b. *N. Engl. J. Med.* 295:1287-91, 1976.
18. Carney, J.A., Sizemore, G.W., and Lovestedt, S.A.: Mucosal ganglioneuromatosis, medullary thyroid carcinoma, and pheochromocytoma: multiple endocrine neoplasia, type 2 b. *Oral Surg.* 41:739-52, 1976.
 19. Chong, G.C., Behrs, O.H., Sizemore, G.W., and Woolner, L.H.: Medullary carcinoma of the thyroid gland. *Cancer* 35:695-704, 1975.
 20. Robertson, D.M., Sizemore, G.W., and Gordon, H.: Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 79:772-87, 1975.
 21. Brasfield, R.D. and Das Gupta, T.K.: Von Recklinghausen's disease: a clinicopathological study. *Ann. Surg.* 175:86-104, 1972.
 22. DeQuattro, V. and Chan, S.: Raised plasma-catecholamines in some patients with primary hypertension. *Lancet* 1:806-09, 1972.
 23. Stewart, B.H., Bravo, E.L., Haaga, J., et al.: Localization of pheochromocytoma by computed tomography. *N. Engl. J. Med.* 299:460-61, 1978.
 24. Wallace, J.M. and Gill, D.P.: Prazosin in the diagnosis and treatment of pheochromocytoma. *J.A.M.A.* 240:2752-53, 1978.
 25. Rosei, E.A., Brown, J.J., and Lever, A.F.: Treatment of pheochromocytoma and of clonidine withdrawal hypertension with labetalol. *Br. J. Clin. Pharmacol.* 3:809-15, 1976.
 26. El-Minawi, M.F., Paulino, E., Cuesta, M., and Ceballos, J.: Pheochromocytoma masquerading as pre-eclamptic toxemia. *Am. J. Obstet. Gynecol.* 109:389-95, 1971.
 27. Allen, C.T. and Imrie, D.: Hypoglycemia as a complication of removal of a pheochromocytoma. *Can. Med. Assoc. J.* 116:363-64, 1977.
 28. Wilkins, G.E., Schmidt, N., and Doll, W.A.: Hypoglycemia following excision of pheochromocytoma. *Can. Med. Assoc. J.* 116:367-68, 1977.